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EXAMINER
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ART UNIT	PAPER NUMBER
1642	

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24

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
08/897,441	Fibi et al
Examiner	**Art Unit**
Karen Canella	1642

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3 months* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☐ Responsive to communication(s) filed on _____.

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under ***Ex parte Quayle***, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *5-7, 9-12, and 14-23* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *5-7, 10-12, and 17-23* is/are rejected.

7) ☒ Claim(s) *9 and 14-16* is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☒ Interview Summary (PTO-413) Paper No(s). 23
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. For the reasons stated in the Interview Summary of September 19, 2002, the finality of the Office action of Paper No. 20 is withdrawn.

2. Claims 5-7, 9-12, and 14-23 are under consideration.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

4. Claims 9, 11, 15, 16, 20 and 21 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

Claim 11 fails to further limit claim 6. Claim 11 is drawn to a diagnostic aid containing the antibody of claim 6 without inclusion of an additional embodiment to further limit the claim. The recitation of "diagnostic aid" does not constitute a specific embodiment.

Claims 20 and 21 fail to further limit the scope of claim 17 as claims 20 and 21 are drawn to one or more antibodies and are thus larger in scope than claim 17 drawn to "an antibody" in the singular form, versus "antibodies" in the plural form, and further because the recitation of "diagnostic aid" and "pharmaceutical composition" without inclusion of additional embodiments does not further limit the claims.

Claims 9, 15 and 16 fail to limit the scope of claim 6. Claim 6 is drawn to an antibody directed against an EPO peptide. Claims 9, 15 and 16 encompass anti-idiotypic antibodies to the antibody of claim 6. The anti-idiotypic antibodies are not a subset of the antibodies of claim 6 as they would not be able to bind the EPO peptides and therefore would not result in narrowing the scope of claim 6,.

Claim 16 fails to further limit the scope of claim 9 as the recitation of a "diagnostic aid" does not constitute a description of further embodiments.

5. Claim 21 is objected to under 37 CFR 1.75 as being a substantial duplicate of claim 20. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k). Without a recitation of specific limitations pertaining to a diagnostic aid and pertaining to a pharmaceutical composition, the claims have an identical scope which does not further limit the scope of claim 6.

6. Claim 23 is objected to under 37 CFR 1.75 as being a substantial duplicate of claim 6. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k). Claim 23 is drawn to the antibody of claim 6 which is directed at epitopes which bind to the EPO receptor and as such has the same scope as claim 6 since it provides no embodiments which would limit the antibodies of claim 6 and since all of the antibodies of claim 6 bind to epitopes in EPO which bind to the EPO receptor..

7. Claims 10, 12 and 22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention

(A) Claim 12 lacks antecedent basis in claim 5, as claim 5 is drawn to a method, not a product.

(B) Claims 10 lacks antecedent basis in claim 6, as claim 6 is drawn to a product and claim 10 is drawn to a method.

(C) Claim 22 lacks antecedent basis in claim 17 as claim 22 is drawn to a method and claim 17 is drawn to a product.

(D) Claim 22 provides for the use of one or more antibodies of claim 17, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

8. Claims 10 and 22 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claims 10 and 22 are drawn to methods for purifying EPO, an EPO derivative or an EPO peptide. The claim relies on EPO derivatives. The written description sets forth only EPO peptides on page 3, lines 29-35. The specification mentions but does not teach EPO derivatives, nor does the specification define the genus of EPO derivatives, or provide any examples of EPO derivatives.

The disclosure of a single species may provide an adequate written description of a genus when the species disclosed is representative of the genus. The instant claims encompass full length functional EPO, full length denatured EPO, full length mutant EPO, EPO variants such as truncation mutations, splice variants, allelic variants, which are both functional and non-functional, as well as fragments of EPO which are not fully described. In addition, the instant claims encompass every type of chemical modification which can be carried out on a protein sequence. There is substantial variability among the species of variants encompassed within the scope of the claims because full length normal EPO is only one species descriptive of EPO derivatives. Thus the claims encompasses a genus with widely varying attributes. Furthermore, because the specification has not disclosed or contemplated a specific chemical or protein moiety, the addition of which to full length EPO would constitute an EPO "derivative", full length EPO itself is not representative of a genus of derivatives as no information regarding the chemical structure of an auxiliary moiety attached to EPO has been described.

A description of a genus of molecules may be achieved by means of recitation of a representative number of molecules, defined by structure, falling within the scope of the genus or a recitation or structural features common to members of the genus, which features constitute a substantial portion of the genus. (Reagents of the University of California v. Eli Lilly, 119 F3d 1559, 1569, 43 USPQ2d 1398-1406, Fed. Cir. 1997).

The written description sets forth the EPO peptides on page 3, lines 29-35, that would be part of some members of the genus, and the art at the time of filing is enabling for full length human EPO and murine EPO. Since the claimed genus encompasses full length EPO proteins beyond human and murine EPO,, in addition to mutants, variants and fragments, etc. attached to undisclosed chemical moieties, the disclosed peptide entities and full length human and murine EPO do not "constitute a substantial portion" of the claimed genus. Therefore, the specification does not provide adequate written description of the claimed genus of EPO derivatives.

9. The rejection of claims 17 and 18 under 35 U.S.C. 102(b) as being anticipated by Sytkowski et al (Journal of Biological Chemistry, 1987, Vol. 262, pp. 1161-1165) is maintained for reasons of record. The rejection of claims 20 and 21 under 35 U.S.C. 102(b) as being anticipated by Sytkowski et al (Journal of Biological Chemistry, 1987, Vol. 262, pp. 1161-1165) is made for reasons of record. Claim 17 is drawn to an anti-erythropoietin (EPO) antibody directed against epitopes that bind to the EPO receptor. Claim 18 embodies the antibody of claim 17 wherein said antibody neutralizes the biological activity of EPO. Claim 20 is drawn to a "diagnostic" aid containing one or more anti-EPO antibodies of claim 17 for the detection of EPO. Claim 21 is drawn to a "pharmaceutical composition" containing one or more anti-EPO antibodies of claim 17. Please note again that neither "diagnostic aid" nor "pharmaceutical composition" constitutes a claim limitation, and recitation of the intended use of "detection of EPO" does not impart patentable distinctness to a product.

Sytkowski discloses anti-peptide 99-118 and anti-peptide 111-129 which inhibit the action of erythropoietin by direct interaction with the receptor-binding domain of erythropoietin (page

1163, table 2, page 1164, second column, last paragraph, line 16 to page 1165, first column, line 7 and lines 15-19). The specification states on page 2, line 33 to page 3, line 4 that the neutralizing antibodies of Sytkowski bind to the receptor domain. Thus Sytkowski anticipates claims 17 and 18, and due to the lack of specific limitations for "diagnostic aid" and "pharmaceutical composition", claims 20 and 21 which are not patentably distinct from the antibodies of claim 17.

Applicant argues that the peptides used to raise the antibodies to residues 111-129 do not themselves bind to EPO and therefore these peptides cannot represent epitopes which bind to EPO receptor. Applicant argues that the six peptides used by Sytkowski failed to inhibit the biological activity of whole EPO. It is noted that applicant is arguing limitations that are not part of the claims. Applicant has drawn attention to page 1162, right column first full paragraph of Sytkowski et al to substantiate the above arguments. This has been considered but not found to be persuasive. In the cited paragraph of Sytkowski there is described an experiment wherein a synthetic homolog (page 1162, second column, first full paragraph, lines 1-3) of the 111-129 peptide was used in an in vitro assay to measure receptor activation and/or competition with natural EPO. On page 1161, (second column, lines 1-5, under the heading "Synthetic Peptides") it is noted by Sytkowski that it was necessary to attach a tyrosine residue to the amino terminus to three of the peptides in order to permit radio iodination of the peptides for the in vitro assay. Lines 11-13 of that paragraph indicate that the 111-129 peptide was one such peptide that was modified for the assay. Thus, the result reported for direct binding to the EPO receptor was for a peptide consisting of tyrosine and the 111-129 peptide, not solely a peptide consisting of residues 111-129. Sytkowski discloses that anti-peptide 111-129 neutralized EPO biological activity and that this neutralization could be reversed by excess peptide, demonstrating that the observed inhibition was due to antigen-specific binding to erythropoietin (page 1104, first column, first full paragraph, lines 9-18). Furthermore, the instant claims are drawn to an antibody directed against an epitope which binds to the EPO receptor and as such do not require that an isolated peptide consisting of said epitope or comprising said epitope be required to possess the biological activity

of the parent protein, EPO. Applicant argues that epitopes are specific portions of a protein to which antibodies bind and that the demonstration by Sytkowski proves that the peptide 111-129 does not bind the EPO receptor. This is not persuasive for the reasons set forth above, that Sytkowski used a s peptide homolog to the 11-129 peptide when measuring binding to the EPO receptor in vitro, and further, because the claims do not contain limitations which require the isolated peptide used to rise the antibody to bind the EPO receptor or have any other biological activity, It is well-know in the art that antibodies bind three-dimensional structures and are therefore not confined to binding a linear peptide. Paul (Fundamental Immunology, 1993) states that "Antigenic sites consisting of amino acid residues that are widely separated in the primary protein sequence but brought together on the surface of a protein by the way it folds in its native conformation have been called "assembled topographic sites" because they are assembled from different parts of the sequence an exist only in the surface topography of the native molecule. By contrast the sites that consist of only a single continuous segment of protein sequence have been called "segmental antigenic sites". Thus an epitope, the site of binding with an antibody paratope can be a continuous peptide fragment or not. Claim 17 is drawn to antibodies directed against an epitope that binds to the EPO receptor and can read on any antibody that so binds, regardless of whether or not the epitope can be simulated within a linear sequence or exist only in the three-dimensional structure of EPO. Moreover, this argument from applicant is in conflict with the teachings of the specification on page 2, line 33 to page 3, line 4 which states,

> "antibodies directed against some of these EPO peptides , have already been disclosed by Sytkowski and Donahue, J Biol. Chem. 262 (1987), 1161-1165. Antibodies which were able to neutralize the biological acitivity of EPO are prepared by Sytkowski and Donahue only with EPO peptide which correspond to positions 99-118 and 111-129. The authors conclude from this that the (single) receptor binding domain is located in the region of amino acid positions 99 to 129 of EPO."

Applicant ends this argument by stating that the antibodies raised to the 111-129 peptide do in fact bind to the full length APO protein. However, instant claims 17-19 read on any antibody which binds to an epitope which binds to the EPO receptor, and are not confined to epitopes that can be reproduced by short peptides retaining the biological activity of EPO.

Applicant argues that the finding of Philo et al and Nahri et al demonstrating that the EPO receptor undergoes a conformational change when bound by EPO are mere conjecture. However, the findings of Philo et al and Nahri et al demonstrate the complexity of the interaction of EPO with its receptor. It is maintained that due to this complexity it may not be possible for a small peptide to mimic the biological action of erythropoietin.

Applicant concludes by stating that the rejection is faulty because Sytkowski acknowledges that his peptides do not directly bind to EPO. As stated above, the claim is drawn to antibodies and it is not it is not required for the isolated peptides to bind to EPO, and further, Sytkowski used a homologous peptide having an extraneous tyrosine on the amino terminus to measure the binding of the peptide; moreover, the specification concedes that the antibodies made by Sytkowski bind to the EPO receptor binding domain.

10. The rejection of claim 10 under 35 U.S.C. 103(a) as being unpatentable over Sytkowski et al (Journal of Biological Chemistry, 1987, Vol. 262, pp. 1161-1165) in view of Yanagawa et al (Blood, 1984, Vol. 64, pp. 357-364) is withdrawn.

11. The rejection of claim 19 under 35 U.S.C. 102(b) as being anticipated by Sytkowski et al (Journal of Biological Chemistry, 1987, Vol. 262, pp. 1161-1165) is withdrawn.

12. Claims 17, 18, 20-22 are rejected under 35 U.S.C. 102(b) as being anticipated by Wojchowski et al (Biochimica et Biophysica Acta, 1987, Vol. 913, pp. 170-178) as evidenced by Sytkowski et al (Journal of Biological Chemistry, 1987, Vol. 262, pp. 1161-1165). Claim 22 is drawn to a method of purifying EPO by using one or more anti-EPO antibodies of claim 17.

Wojchowski et al disclose a method of purifying EPO using an immunoaffinity column comprising anti-111-129 antibodies (page 171, under the heading "Antibodies" and page 172 under the headings "Immunoaffinity medium" and "Purification of human urinary erythropoietin").

Wojchowski et al does not specifically disclose that the anti-111-129 antibodies are directed against epitopes that bind to the EPO receptor or neutralize the biological activity of EPO.

Sytkowski discloses anti-peptide 111-129 antibodies which inhibit the action of erythropoietin by direct interaction with the receptor-binding domain of erythropoietin (page 1163, table 2, page 1164, second column, last paragraph, line 16 to page 1165, first column, line 7 and lines 15-19). The specification states on page 2, line 33 to page 3, line 4 that the neutralizing antibodies of Sytkowski bind to the receptor domain. Thus Sytkowski anticipates claims 17 and 18, and due to the lack of specific limitations for "diagnostic aid" and "pharmaceutical composition", claims 20 and 21 which are not patentably distinct from the antibodies of claim 17. Thus the method of purifying EPO using anti-111-129 antibodies inherently comprises antibodies with the characteristic of neutralizing the biological activity of EPO and binding epitopes which bind the EPO receptor, for the reasons set forth above.

13. The rejection of claims 5, 6, 11, 12, 17, 20 and 23 under 35 U.S.C. 102(b) as being anticipated by Lin (US 4,703,008) is maintained for reasons of record. The rejection of claims 18 and 21 under 35 U.S.C. 102(b) as being anticipated by Lin (US 4,703,008) is made for reasons of record. Claim 6 is drawn in part to an antibody directed against an erythropoietin peptide, wherein said antibody neutralizes the biological activity of EPO and wherein said EPO peptide consists essentially of a peptide of 152 to 166(P2/1). Claim 5 is drawn in part to a method of using erythropoietin peptide consisting essentially of 152 to 166 (P2/1) for the preparation of epitope-specific anti-EPO antibodies, said method comprising immunizing an animal with said peptide and isolating said epitope-specific anti-EPO antibodies. Claim 11 is drawn to a diagnostic aid comprising an antibody of claim 6. Claim 12 is drawn to a diagnostic aid containing and EPO peptide as defined in claim 5. Please note that the recitation of "diagnostic aid" does not constitute a further embodiment of the claimed antibody or peptide and that the recitation of the intended use of said antibody or peptides does not confer patentable distinctness to the products.

Claim 23 is drawn to an anti-EPO antibody of claim 6 which is directed to epitopes which bind to the EPO receptor.

Claim 17 is drawn to an anti-erythropoietin antibody directed against epitopes that bind to the EPO receptor. Claim 18 embodies the antibody of claim 17 wherein said antibody neutralizes the biological activity of EPO. Claim 20 is drawn to a "diagnostic" aid containing one or more anti-EPO antibodies of claim 17 for the detection of EPO. Claim 21 is drawn to a "pharmaceutical composition" containing one or more anti-EPO antibodies of claim 17. Please note again that neither "diagnostic aid" nor "pharmaceutical composition" constitutes a claim limitation, and recitation of the intended use of "detection of EPO" does not impart patentable distinctness to a product.

Lin discloses a method of using erythropoietin peptides consisting of essentially of residues 152-166 for the preparation of epitope-specific anti-EPO antibodies comprising immunization of rabbits with the peptide 144-166 (column 35, lines 21-34). Lin discloses the diagnostic uses of the 144-166 peptide (column 35, line 58 to column 36, line 20). Lin does not specifically disclose that said antibodies were isolated, however, Lin states that the resulting serum antibodies were used to immunoprecipitate 125-I labeled EPO, therefore, it is evident that the antibodies produced by immunization of rabbits with the 144-166 peptide were isolated from the rabbits. Thus Lin anticipates claim 17, and 20 and 21, for the reasons stated above, namely, the recitations of "diagnostic aid" and "pharmaceutical composition" alone do not constitute further embodiments to claims 20 and 21. Lin do not disclose that the antibodies produced from the 144-166 peptide would contain neutralizing antibodies, however, it would be inherent in the anti-144-166 antibodies that a subset of antibodies would be neutralizing as the instant specification is claiming that anti-152-166 antibodies are neutralizing. Therefore, Lin anticipates claim 18, and further claim 6, and the antibodies produced thereby as in claim 5 as well as claims 11 and 23 which have the same scope as claim 6, for the reasons stated above, that claims 11 and 23 do not contain further limitations that would narrow the scope of claim 6. Lin discloses the

diagnostic uses for the 144-166 peptide, therefore anticipating claim 12 (column 35, line 58 to column 36, line 20).

Applicant argues that the 144-166 peptide used by Lin does not exhibit biological activity and therefore cannot be an epitope. Applicant states that conclusory statements based on general knowledge or common sense cannot be used to overcome the deficiencies of a reference. However, the examiner was using "common sense" to counter the argument of applicant regarding the lack of biological activity of the isolated peptide. The arguments used by the examiner were not necessary to make the rejection of the instant claims, especially since applicant is arguing limitations that are not part of the claims., such as the requirement of the isolated epitope to possess the same biological activities as the native protein. Lin states that "preliminary in vivo activity studies on the three peptides revealed no significant activity either alone or in combination" has no bearing whatsoever on the antibodies which were raised against these proteins. There is no requirement in the claims for any biological activity attributable to the peptides used to generate the claimed antibodies. Applicants argue that the examiner has not met the high standards of the U.S. Court of Appeals in the allegation that the method of using an erythropoietin peptide for the preparation of epitope-specific anti-EPO antibodies, an epitope being defined as being composed or one or more peptides, or one or more sections of peptide sequence, wherein said EPO peptide consists essentially of amino acid positions 152 to 166 would inherently comprise the method of using the erythropoietin 144-166 peptide disclosed by Lin. The essential argument seems to be weather of not "consisting essentially of a peptide less than the complete erythropoietin sequence....consisting of 152-166" would be inherently comprised by the 144-166 peptide of Lin. The M.P.E.P (2111.03) states

For the purposes of searching for and applying prior art under 35 U.S.C. 102 and 103, absent a clear indication in the specification or claims of what the basic and novel characteristics actually are, "consisting essentially of" will be construed as equivalent to "comprising." See, e.g., PPG, 156 F.3d at 1355, 48 USPQ2d at 1355 ("PPG could have defined the scope of the phrase consisting essentially of' for purposes of its patent by making clear in its specification what it regarded as constituting a material change in the basic and novel characteristics of the invention."). See also In re Janakirama-Rao, 317 F.2d 951, 954, 137 USPQ 893, 895-96 (CCPA 1963). If an applicant contends that additional steps or materials in the prior art are excluded by the recitation of "consisting essentially of," applicant has the burden of showing that the introduction of additional steps or components would materially change the characteristics of applicant's invention. In re De Lajarte, 337 F.2d 870, 143 USPQ 256 (CCPA 1964). See also Ex parte Hoffman, 12

USPQ2d 1061, 1063-64 (Bd. Pat. App. & Inter. 1989) ("Although consisting essentially of' is typically used and defined in the context of compositions of matter, we find nothing intrinsically wrong with the use of such language as a modifier of method steps. . . [rendering] the claim open only for the inclusion of steps which do not materially affect the basic and novel characteristics of the claimed method. To determine the steps included versus excluded the claim must be read in light of the specification. . . . [I]t is an applicant's burden to establish that a step practiced in a prior art method is excluded from his claims by consisting essentially of' language.").

Thus, according to the M.P.E.P., it is applicants burden, not the examiners, to prove that the method of Lin would not anticipate the instant claimed method.

Applicant argues that "the fact that Lin's 144-166 peptide has no in vivo activity support the notion that this peptide does not present the 152-166 epitope properly. Again, this is not persuasive, as limitations regarding the biological activity of the peptide used to raise the antibody are not part of the instant claims. Lin does not specifically disclose that the polyclonal antibodies obtained by immunization with the 144-166 peptide have EPO neutralizing activity. However, it is reasonable to conclude that some of the antibodies which constitute the polyclonal antibodies made by Lin would have the property of reacting with the epitope of EPO consisting of residues 152-166, as these amino acids are included in residues 144-166 and that these antibodies would inherently be neutralizing antibodies, as the specification teaches that the property of binding to residues 152-166 of EPO is commensurate with the property of a neutralizing antibody.

Claim 17 does not specify that the isolated peptide used to simulate an epitope of the full length EPO protein must bind to the EPO receptor in vivo and elicit a biological effect. There are many reasons why a peptide administered in vivo would not elicit the same biological effect of the parent protein. Firstly, the peptide, out of context of the EPO protein may be rapidly degraded in vivo before binding to the EPO receptor. Secondly, the binding of other epitopes, not included in the peptide used to raise an antibody, may be necessary for increasing the binding affinity of the isolated peptide by altering the steric interaction of residues 144-166 with the EPO receptor, for the reasons given in Philo et al and Narhi et al, supra. The specification teaches that the peptide 152-166 represents an amino acid sequence within EPO which directly binds to the EPO receptor. The peptide used by Lin, 144-166, is the same amino acid sequence with the addition of the eight amino acid sequences which are normally attached to the animo terminus of

the 152-166 sequence in the full length EPO protein. As antibodies raised to the 152-166 peptide directly bind the EPO receptor, it is reasonable to conclude that a subset of antibodies raised to the 144-166 peptide also directly binds to the EPO receptor as it contains the 152-166 sequence in addition to adjacent amino acid sequences present in EPO. Further any antibodies which would bind to the residues of 152-166 of EPO would inherently be neutralizing antibodies, as the specification teaches that the property of binding to residues 152-166 of EPO is commensurate with the property of a neutralizing antibody.

14. Claims 17-21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sytkowski et al (Journal of Biological Chemistry, 1987, Vol. 262, pp. 1161-1165) in view of Kaplan et al (Monoclonal Antibodies in clinical Medicine, 1982, pp. 1-2). The embodiments of claims 17, 18 and 20 and 21 are taught by Sytkowski et al for the reasons set forth in section 8, above. Claim 19 is drawn to the antibody of claim 17, wherein said antibody is monoclonal. Sytkowski et al teach polyclonal antiserum of claim 17. Sytkowski et al do not teach a monoclonal antibody.

Kaplan et al teach the advantages of monoclonal antibodies produced by hybridomas include monoclonality, monospecificity and permanent availability (page 1, lines 3-7).

It would have been *prima facia* obvious to one of ordinary skill in the art at the time the claimed invention was made to raise monoclonal antibodies to the 111-129 peptide. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of Kaplan et al on the general advantages associated with the production and use of monoclonal antibodies relative to antiserum.

15. Claims 5-7, 10-12 and 17-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Miyazaki et al (Journal of immunological Methods, 1988, Vol. 113, pp. 261-267). The specific embodiments of claims 5, 6, 11, 12, 17, 18, 20, 21 and 23 are taught by Lin et al for the reasons set forth in section 13 above.

Claim 7 is drawn to the antibody of claim 6, wherein said antibody is monoclonal. Claim 10 is drawn to a method of using the antibodies of claim 6 for purifying EPO, EPO derivative or EPO peptide comprising contacting a biological sample with said antibody where said antibody is bound to a carrier material suitable for chromatography and isolating said EPO, EPO derivative or EPO peptide. Claim 19 is drawn to the antibody of claim 17, wherein said antibody is monoclonal.

Miyazaki et al teach monoclonal antibodies against human erythropoietin, and immunoaffinity columns comprising said monoclonal antibodies and a method of purifying EPO comprising contacting a biological sample with said immunoaffinity column (page 262, under the heading "Materials and methods" and page 263, under the sub-headings "Preparation of an immunoaffinity column" and "Preparation of natural HuEPO"). Miyazaki et al teach the immunoaffinity purification of native EPO by monoclonal antibodies which react with native EPO versus denatured EPO is more desirable than previous methods necessitating the denaturation of EPO before purification page 262, first column, lines (page 267, last two sentences) and more desirable than a previous method using immunoaffinity purification based on monospecific antibodies rather then monoclonal antibodies, wherein said method provided a EPO with reduced biological activity in vivo ((page 261, second column, line 13 to page 262, line 11). Lin et al teaches the specific embodiments of claims 5, 6, 11, 12, 17, 18, 20, 21 and 23 for the reasons set forth above. Lin et al teach that the anti-144-166 antiserum was able to bind human urinary EPO (column 36, lines 27-33). Lin et al suggest but does not teach a methods wherein the 144-166 peptide be used to generate monoclonal antibodies useful in the affinity purification of EPO and EPO-related products (column 35, line 1 to column 36, line 19).

It would have been *prima facia* obvious to one of ordinary skill in the art at the time the claimed invention was made to substitute the 144-166 peptide for the E-rHuEPO and C-rHuEPO used as the immunizing antigen in the method of Miyazaki et al. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of

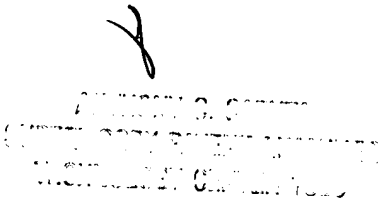
Miyazaki et al on the superiority of immunoaffinity columns based on monoclonal antibodies which bind to undenatured EPO.

16. Claim 14 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

17. The rejection of claims 6, 7, 11, 17-21 for obviousness-type double patenting over claims 1 and 2 of USP 5,712,370 is maintained for reasons of record.

Conclusion

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen Canella whose telephone number is (703) 308-8362. The examiner can normally be reached on Monday through Friday from 8:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308-3995. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.



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